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UNDERSTANDING THE DISEASE

Right ventricular-protective ventilation in ARDS: thinking beyond lung protection

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Epidemiologic data demonstrate that patients with moderate–severe acute respiratory distress syndrome (ARDS) who develop right ventricular (RV) injury (including RV dilatation, dysfunction, and limitation) are at increased risk of mortality [1, 2]. Despite advances in supportive care, clinicians continue to struggle to improve outcomes in ARDS. Consequently, RV protection has emerged as an important treatment goal, distinct from strategies focused on lung and diaphragm protection. This article will address two fundamental questions: (1) What constitutes RV-protective ventilation in ARDS? and (2) How might RV-protective ventilation conflict with the principles of lung-protective ventilation?

Right ventricular injury in ARDS

ARDS is characterized by numerous pathophysiologic and treatment-related factors that cumulatively increase RV afterload, defined as the threshold load that must be overcome to open the pulmonic valve and initiate ejection [3]. In patients with RV limitation (limitation of RV filling), even modest increases in afterload lower RV stroke volume, and in turn, left ventricular stroke volume [4]. Moreover, repetitive or sustained exposure to increased RV afterload may result in decreased RV contractility (RV dysfunction) or acute cor pulmonale (ACP), defined echocardiographically by RV dilatation and septal dyskinesia [5]. These RV injury phenotypes increase the risk of hemodynamic instability, systemic venous congestion [6], and end-organ hypoperfusion. Collectively, these phenomena represent an under-investigated causal pathway underpinning ARDS mortality.

RV afterload increases due to hypoxemia, hypercapnia, microvascular thrombosis, and decreased pulmonary compliance due to reduced size of the "baby" lung. Hypoxemia and hypercapnia cause direct pulmonary vasoconstriction and, thereby, raise pulmonary vascular resistance. Downstream interruption of pulmonary blood flow occurs due to microvascular thrombosis and the way mechanical ventilation is set [7]. Reduced baby lung size means that even a "protective" tidal volume of 6 ml/kg predicted body weight may result in elevated end-inspiratory transpulmonary pressure that causes critical closure of intra-alveolar vessels and West Zone 1 or 2 (non-Zone 3) conditions that increase RV afterload. Alveolar collapse and overdistension represent distinct but overlapping processes that can increase RV afterload. Overdistension increases the risk of non-Zone 3 conditions whereas collapse increases local hypoxic pulmonary vasoconstriction and implies loss of available lung size. Moreover, collapsed lung units are prone to cyclic opening and closing (atelectrauma) that promotes a pro-inflammatory milieu that can worsen lung injury and further decrease lung compliance. Supporting this concept, experimental lung injury models have shown that aggressive avoidance of overdistension may induce substantial atelectasis, hemodynamic instability and increased mortality [8].

A ratio of partial pressure of oxygen in arterial blood to the fraction of inspiratory oxygen concentration (PaO_2/FiO_2) < 150 mmHg is an independent risk factor for acute cor pulmonale in ARDS [5]. The mechanism for this is likely that the greater impairment in oxygenation correlates with decreased baby lung size and the extent of non-Zone 3 conditions during ventilation.

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Likewise, an arterial partial pressure of carbon dioxide ($PaCO_2$) ≥ 48 mmHg also predicts ACP [5], indicating the deleterious effects of pulmonary vasoconstriction and decreased ventilatory efficiency of the injured lung that result in clinicians administering greater transpulmonary driving pressure to provide "acceptable" ventilation. Driving pressure ≥ 18 cmH_2O is independently associated with ACP risk [5]. The magnitude of RV afterload increases during inspiration and correlates with tidal volume and driving pressure [7]. Pneumonia is also a risk factor for ACP likely because "pulmonary ARDS" classically causes a significant reduction in the baby lung size.

Lung-protective vs RV-protective ventilation: overlap and tensions

RV-protective ventilation must minimize exposure to tidal increases in RV afterload while maintaining adequate gas exchange and oxygen delivery to peripheral tissues (Fig. 1, Panel I). Traditional lung-protective ventilation may conflict with RV protection principles. Positive end-expiratory pressure (PEEP) titrated to oxygenation may lead the clinician to provide higher PEEP that exposes patients to alveolar overdistension, greater RV afterload, and greater risk of RV injury. Given the significant heterogeneity in lung recruitability in ARDS, a key initial step in selecting a ventilatory strategy is to assess the potential for lung recruitment. Titration of PEEP guided by bedside tools including the recruitment to inflation ratio or electrical impedance tomography (Fig. 1, Panel II) allows for optimization of lung recruitment that will increase the available lung size in recruitable patients and limit tidal alveolar overdistension, a phenomenon that is associated with increased RV afterload in experimental and clinical studies [9, 10].

Prescribing ventilation based on tidal volume per predicted body weight may also be deleterious to RV biomechanics in patients with reduced lung compliance. Instead, tidal volume should be prescribed based on a patient's available lung size. At the bedside, this is estimated as the respiratory system compliance and driving pressure, the ratio of tidal volume to compliance, has emerged as a primary target for lung protection. Based on physiological reasoning and epidemiological data [5], driving pressure should be limited to optimize RV protection as well [5, 7]. However, driving pressure reduction must be balanced with secondary hypercapnia that may increase pulmonary vasoconstriction. Furthermore, increasing respiratory rate—a strategy that is encouraged to facilitate plateau and driving pressure reduction [11]—may theoretically be deleterious to RV function, when expiratory time becomes insufficient, by promoting intrinsic PEEP and exposing the RV to peak afterload over more respiratory cycles per minute. Conversely, reducing respiratory rate may increase hypercapnia which can raise pulmonary vascular resistance and thereby increase RV afterload. Broad recommendations for ventilatory strategies that emphasize permissive hypercapnia may be deleterious to RV function in selected patients. Given these competing physiological considerations, there is currently insufficient clinical evidence to suggest that a strategy of lowering respiratory rate is independently RV-protective.

Preservation of spontaneous efforts during assisted ventilation may lower RV afterload, for a given transpulmonary driving pressure, compared to passive ventilation. These were the findings of a physiologic study performed in post-operative cardiac surgery patients [12]. These findings require further investigation as severe lung injury is associated with large inspiratory efforts that result in significant end-inspiratory transpulmonary pressure and the possibility of aggravated

(See figure on next page.)

Fig. 1 **(I)** This schematic summarizes a physiology-based approach to mechanical ventilation, highlighting strategies that protect both the lungs and right ventricle. It emphasizes the dynamic balance between optimizing gas exchange, minimizing ventilator-induced lung injury, and supporting cardiac function, with consideration of adjunctive therapies in severe or refractory cases. **(II)** This panel is composed of original figures derived from the authors' research programs (McGill University Health Centre and University Hospitals of Leicester NHS Trust) and illustrates the causal pathway by which complementary monitoring modalities inform right ventricular physiology and guide ventilatory titration. Titrating positive end-expiratory pressure to an oxygenation target may lead to excessive alveolar overdistension (**A**) compared to an electrical impedance tomography-guided approach that minimizes alveolar overdistension and collapse (**B**). Monitoring airway pressure (**C**) and esophageal pressure (**D**) allows clinicians to quantify lung stress (transpulmonary pressure (**E**)) and monitor the tidal increase in transpulmonary pressure (**F**) to minimize right ventricular afterload. Right ventricular afterload can be monitored by simultaneously tracking the pulmonary artery pressure (**G**) and right ventricular pressure (**H**) and calculating the right ventricular isovolumetric contraction pressure (**I**) which is the difference between the diastolic pulmonary artery pressure and right ventricular end-diastolic pressure. Altogether, a personalized, physiology-based approach rooted in multimodal cardiopulmonary monitoring may decrease the risk of developing acute cor pulmonale (**J**) and decrease mortality in patients with ARDS. ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; IMV, invasive mechanical ventilation; PBW, predicted body weight; PEEP, positive end-expiratory pressure; P_{plat}, plateau pressure; RV, right ventricle/right ventricular; VV ECMO, venovenous extracorporeal membrane oxygenation; VP ECMO, venopulmonary extracorporeal membrane oxygenation; VVA ECMO, venovenoarterial extracorporeal membrane oxygenation

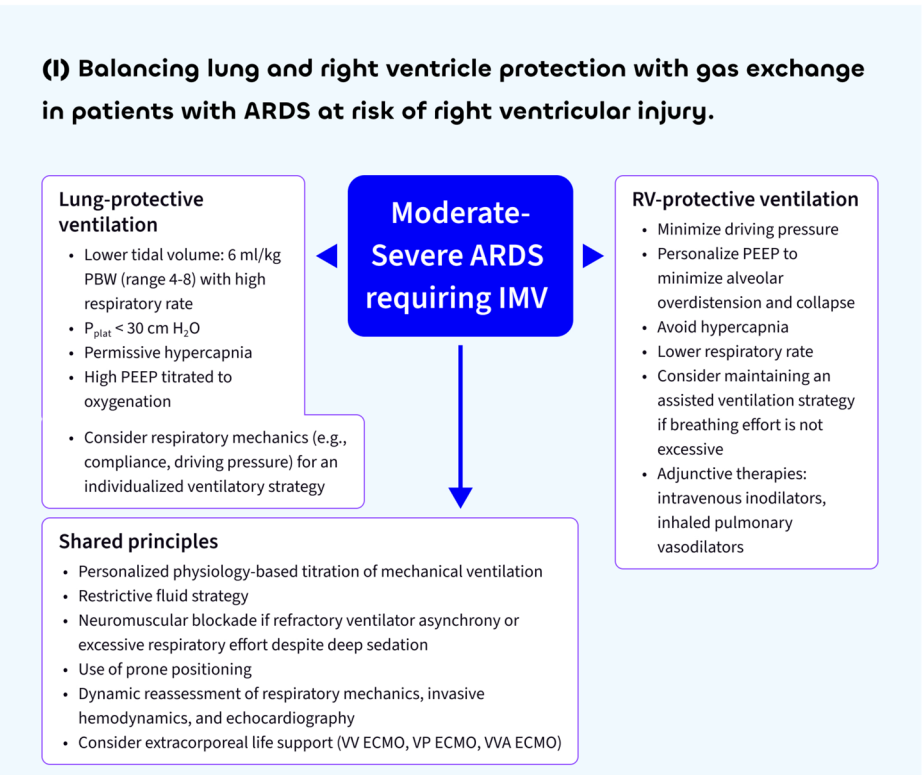
(I) Balancing lung and right ventricle protection with gas exchange in patients with ARDS at risk of right ventricular injury.
Moderate-Severe ARDS requiring IMV
Lung-protective ventilation
• Lower tidal volume: 6 ml/kg PBW (range 4-8) with high respiratory rate
• P_{plat} < 30 cm H_2O
• Permissive hypercapnia
• High PEEP titrated to oxygenation
• Consider respiratory mechanics (e.g., compliance, driving pressure) for an individualized ventilatory strategy
RV-protective ventilation
• Minimize driving pressure
• Personalize PEEP to minimize alveolar overdistension and collapse
• Avoid hypercapnia
• Lower respiratory rate
• Consider maintaining an assisted ventilation strategy if breathing effort is not excessive
• Adjunctive therapies: intravenous inodilators, inhaled pulmonary vasodilators
Shared principles
• Personalized physiology-based titration of mechanical ventilation
• Restrictive fluid strategy
• Neuromuscular blockade if refractory ventilator asynchrony or excessive respiratory effort despite deep sedation
• Use of prone positioning
• Dynamic reassessment of respiratory mechanics, invasive hemodynamics, and echocardiography
• Consider extracorporeal life support (VV ECMO, VP ECMO, VVA ECMO)
(II) Personalized Physiological Monitoring to Optimize Cardiopulmonary Function in ARDS
Electrical impedance tomography
Esophageal pressure monitoring
Invasive pulmonary hemodynamic monitoring
Echocardiography

Fig. 1 (See legend on previous page.)

pulmonary vascular shear stress induced by cyclic, sequential increases in RV preload and afterload [13].

Several components of ARDS management are protective to both the lungs and RV (Fig. 1). Avoidance of alveolar overdistension or collapse represents common ground. Prone positioning lowers mortality in moderate–severe ARDS and is associated with greater cardiovascular failure-free days. Physiologic studies demonstrated that prone positioning can increase cardiac output among patients who manifest ACP in the supine position [14], due to improvement in respiratory mechanics. Prone positioning can also increase venous return, RV preload and cardiac output in patients who are volume responsive in the supine position. Inhaled vasodilatory medications can improve hypoxemia and reduce pulmonary vascular resistance but their use has not been linked to any mortality benefit when applied to undifferentiated patients with ARDS. Intravenous inotropic therapy can augment RV contractility and restore cardiac output in the setting of increased RV afterload, particularly in the presence of concurrent left ventricular dysfunction, which through ventricular interdependence may further impair RV performance via adverse septal interactions and increased left atrial pressure. If inodilators (dobutamine or milrinone) are administered, it is critical to maintain arterial blood pressure to preserve right coronary perfusion. Extracorporeal membrane oxygenation (ECMO) can directly (e.g., venopulmonary ECMO) or indirectly (e.g., venovenous ECMO) unload the RV, improve gas exchange and facilitate lung rest [15, 16]. Figure 1, Panel II illustrates how clinically available bedside monitoring tools can be used to monitor cardiopulmonary physiology to identify patients at risk of RV injury and response to RV-protective interventions.

Research gaps, future directions and conclusion

Future research must clarify the relative risks and benefits of driving pressure and respiratory rate reduction with development of hypercapnia on RV performance in patients with moderate–severe ARDS. The value of preserving controlled breathing effort during assisted ventilation on RV hemodynamics also requires further study in this setting. Partial neuromuscular blockade and diaphragm stimulation [17] may be complementary in optimizing RV protection, maintaining RV preload and decreasing RV afterload during mechanical ventilation of lung-injured patients. Going forward, studies must continue to refine the definition of RV-centered ventilatory targets, validate bedside RV monitoring tools (Fig. 1, Panel II), and incorporate RV-specific endpoints into interventional trials to advance the provision of physiologically personalized cardiopulmonary support in patients with ARDS.

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Declarations

Conflicts of interest
VZ is the chair, HY co-chair and DS is a member and collaborator of the Protecting the Right Ventricle Network (PRORVNet). DS reports an educational grant from Fisher & Paykel Healthcare, outside the submitted work and VZ reports honoraria for education from Mitsubishi Tanabe Pharma Europe, outside the submitted work. HY is a member of the advisory board for AOP Health.

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